



The association of seizure control with neuropathology in dementia

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Seizures in people with dementia (PWD) are associated with faster cognitive decline and worse clinical outcomes. However, the relationship between ongoing seizure activity and post-mortem neuropathology in PWD remains unexplored. We compared post-mortem findings in PWD with active, remote and no seizures using multicentre data from 39 Alzheimer's Disease Research Centres from 2005 to 2021.

PWD were grouped by seizure status into active (seizures over the preceding 1 year), remote (prior seizures but none in the preceding 1 year) and no seizures (controls). Baseline demographics, cognition, mortality and post-mortem findings of primary and contributing (co-pathologies) Alzheimer's disease (AD), frontotemporal lobar degeneration, Lewy body, vascular pathologies and neurodegeneration were compared among the groups using Pearson's χ^2 test, Fisher's exact test, t-test and ANOVA.

Of 10 474 deceased PWD, active seizure participants suffered the highest mortality among the groups (proportion deceased among the groups: active = 56%, remote = 35%, controls = 34%, $P < 0.001$). Among 6085 (58.1% of deceased) who underwent autopsy, 294 had active, 151 had remote and 5640 had no seizures. PWD and active seizures died at a younger age (active = 75.8, remote = 77.9, controls = 80.8 years, $P < 0.001$) and had more severe dementia (Clinical Dementia Rating score: active = 2.36, remote = 1.90, controls = 1.69, $P < 0.001$). In *post hoc* analyses, those with primary post-mortem diagnosis of AD with active seizures had more severe and later stages of AD pathology and ATN (amyloid, tau and neurodegeneration), as evidenced by Braak stage for neurofibrillary (tau) degeneration and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score density of neuritic (amyloid) plaques, than remote seizure participants and controls. Active seizure participants had more neurodegeneration, evidenced by cerebral atrophy, hippocampal atrophy and locus coeruleus hypopigmentation, than controls.

Among participants with primary post-mortem diagnosis of non-AD, in *post hoc* analyses, active seizure participants had worse AD co-pathology, evidenced by higher Braak stages than remote seizures and controls and a higher Thal phase of beta-amyloid plaques than remote seizure participants. Neurodegeneration (cerebral/hippocampal atrophy) and locus coeruleus hypopigmentation were comparable among the groups.

In both primary post-mortem AD and non-AD diagnoses, frontotemporal lobar degeneration (co)pathology was less prevalent among active seizure participants than controls, while vascular pathology, Circle of Willis atherosclerosis, Lewy body pathology, lobar atrophy and substantia nigra hypopigmentation were comparable among the three groups.

This study shows that active seizures, compared with remote seizures, are associated with earlier death and post-mortem evidence of more severe ATN pathology. Active seizures are associated with more advanced AD pathology in AD and worse AD co-pathology in non-AD dementias. Therefore, clinicians should be vigilant in detecting ongoing seizures, because this could reflect a worse prognosis in PWD.

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Introduction

People with dementia (PWD) frequently experience seizures, with estimates of incidence ranging from 5% to 64%.¹ PWD who have ongoing seizures suffer from an accelerated cognitive decline,^{2–4} worse functional outcomes and premature mortality.⁵

Emerging evidence suggests that seizures can cause neurodegeneration similar to that observed in PWD,^{6,7} and a high proportion of late-onset seizures are attributed to neurodegenerative changes in the brain.⁸ Cortical and hippocampal neuronal hyperexcitability are pathophysiological features of Alzheimer's disease (AD) dementia.⁹ Deranged intracellular calcium and glutamate levels, impaired function of glia and inhibitory neurons, and accumulation of pathological tau and beta-amyloid (A β) aggregates can all lead to disrupted neuronal excitability, increasing seizure susceptibility.⁹ Likewise, neuronal hyperexcitability is observed in non-AD dementias, especially non-AD tauopathies.¹⁰ Phosphorylated tau is associated with aberrant neuronal firing and hyperactivity and γ -aminobutyric acid-mediated hyperexcitability, leading to epileptogenesis.¹⁰ Although the bidirectional relationship between seizures and dementia is increasingly recognized, few studies have directly examined the association between seizures or the lack of seizures and the neuropathology of AD and other types of non-AD dementias.

Understanding the relationship between seizure control and post-mortem histopathology is crucial, because it could explain worse cognition, function and mortality in PWD with seizures. We hypothesized that worse seizure control would be associated with more severe neurodegeneration in PWD. The primary objective of our prospective, multicentre cohort analysis is to investigate the associations among seizure control (classified as active, remote or seizure-free controls) and post-mortem gross neuropathological and histopathological findings of AD pathology, Lewy body pathology, frontotemporal lobar degeneration (FTD), vascular pathology and overall neurodegeneration in PWD.

Materials and methods

Study design

We used longitudinally maintained, multicentre data from 39 Alzheimer's Disease Research Centres (ADRCs) in the USA.^{11–13}

Our cohort included deceased participants recruited and autopsied between September 2005 and December 2021.

Respective ADRCs acquired Institutional Review Board approvals and maintained written informed consent. Our Institutional Review Board deemed the study exempt because it used de-identified data. We used Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Participants

Inclusion and exclusion criteria

Inclusion criteria (Fig. 1) were as follows: (i) death recorded among study participants; (ii) all-cause cognitive impairment at enrolment or during follow-up; (iii) valid reports of active, remote or no seizures at enrolment or during follow-up; and (iv) autopsy recorded. Participants with the following were excluded: (i) seizure status unreported or unknown throughout the length of the study follow-up; (ii) normal cognition throughout the study follow-up; (iii) alive at the most recent study follow-up; or (iv) deceased but did not undergo an autopsy.

Procedures

Seizure groups

In the data, seizure status is categorized as follows: (i) active seizures, defined as recurrent seizures present at least in the preceding 12 months and possibly over a longer period and/or requiring ongoing anti-seizure medication (ASM) treatment; and (ii) remote seizures, defined as seizures that occurred before at least the preceding 12 months with complete resolution and were not requiring ongoing ASM treatment. Those with neither active nor remote seizures served as controls. Controls had cognitive impairment but no history of seizures. Seizure status data were acquired based on participant and co-participant reports, medical records and clinical observation. Data regarding the semiology, electroencephalography or ASM type were not acquired during data collection.

Cognition

All participants in the three groups had objective clinical evidence of dementia or mild cognitive impairment (MCI) diagnosed after

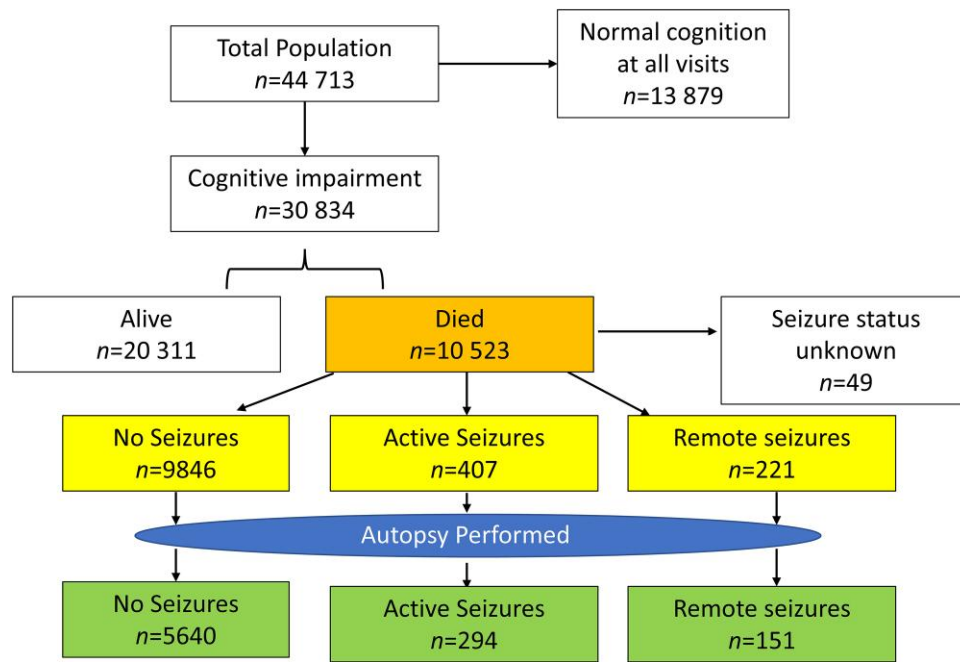


Figure 1 Study flow chart. The flow chart demonstrates that deceased participants who had cognitive impairment prior to death and who underwent autopsy with valid reports of active, remote or no seizures at enrolment or during follow-up were included. Participants who were alive or had normal cognition or seizure status unreported or unknown or who did not undergo autopsy were excluded.

multidisciplinary consensus based on history, neurological examination, an extensive battery of neuropsychological testing, neuroimaging and, at times, biomarkers.

Neuropathology

Histopathology

The ABC scoring system was used to determine AD-related neuropathological changes. The Thal phase for amyloid plaques (A score) was determined by immunohistochemistry to assign a phase (mid-frontal, superior/middle temporal, inferior parietal, hippocampus, entorhinal, basal ganglia, midbrain and cerebellum) and characterized as Phase 0 (A1), 1 (A1), 2 (A1), 3 (A2), 4 (A3) and 5 (A3).¹⁴ Braak staging of neurofibrillary tangles was characterized as Stages I (B1), II (B1), III (B2), IV (B2), V (B3), VI (B3) and 7, defined as the presence of a tauopathy (other than ageing/AD) precluded Braak staging.¹⁴ Braak Stages I and II are called transentorhinal (Fig. 2A), III and IV are called limbic (Fig. 2B), and V and VI are called neocortical (Fig. 2C). Stage 0 implies an absence of neurofibrillary tangles. During Stages I and II (transentorhinal), neurofibrillary tangles involve the entorhinal cortex and hippocampus. During Stages III and IV (limbic), neurofibrillary tangles spread beyond the entorhinal regions to involve the fusiform gyrus, lingual gyrus and neocortical association cortex. Finally, in Stages V and IV, there is widespread neocortical involvement (neocortical).¹⁵ The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score for neocortical neuritic plaque density (plaques with argyrophilic dystrophic neurites, +/- amyloid cores) was categorized into C0 (no neuritic plaques; Fig. 2D), C1 (sparse neuritic plaques; Fig. 2E), C2 (moderate neuritic plaques; Fig. 2F) and C3 (frequent neuritic plaques; Fig. 2G).¹⁴

Lewy body pathology was determined by alpha-synuclein immunohistochemistry to determine whether there was evidence of Lewy body pathology in the olfactory bulb, predominantly amygdala, predominantly brainstem, limbic (transitional), neocortical (diffuse) or no evidence of Lewy body pathology.

FTD and its subtypes were determined, including FTD-tau (Pick's disease), other 3R tauopathies (including MAPT mutation tauopathy), FLD-tau (corticobasal degeneration), FTD-tau (progressive supranuclear palsy), argyrophilic grains, other 4R tauopathies (including sporadic multiple systems tauopathy, globular glial tauopathy, MAPT mutation tauopathy), chronic traumatic encephalopathy, amyotrophic lateral sclerosis (ALS/Parkinsonism-dementia complex of guam), tangle dominant disease and other tauopathies (including unclassifiable, focal, glial only, MAPT mutation tauopathy, not otherwise specified).

Gross findings

Vascular pathology (including ischaemic, haemorrhagic or other strokes, microhaemorrhages, microbleeds, micro-infarcts, lacunes, arteriosclerosis and atherosclerosis of the Circle of Willis) was assessed on gross examination. Evidence of neurodegeneration was determined based on the severity of atrophy (overall cerebral cortex, regional lobar and hippocampi), and substantia nigra hypopigmentation, and locus coeruleus (LC) hypopigmentation on gross examination.

Primary outcome

The primary outcome of the study was to compare the severity of histopathological findings among the three groups (active seizures, remote seizures and control) among participants with neuropathological diagnoses of AD and non-AD dementia. In the secondary analysis, we investigated the association of the seizure group with gross autopsy findings in participants with neuropathological diagnoses of AD and non-AD dementia.

Other variables

Demographic variables of age at death (in years), education (in years), sex (female versus male), race (White versus non-White)

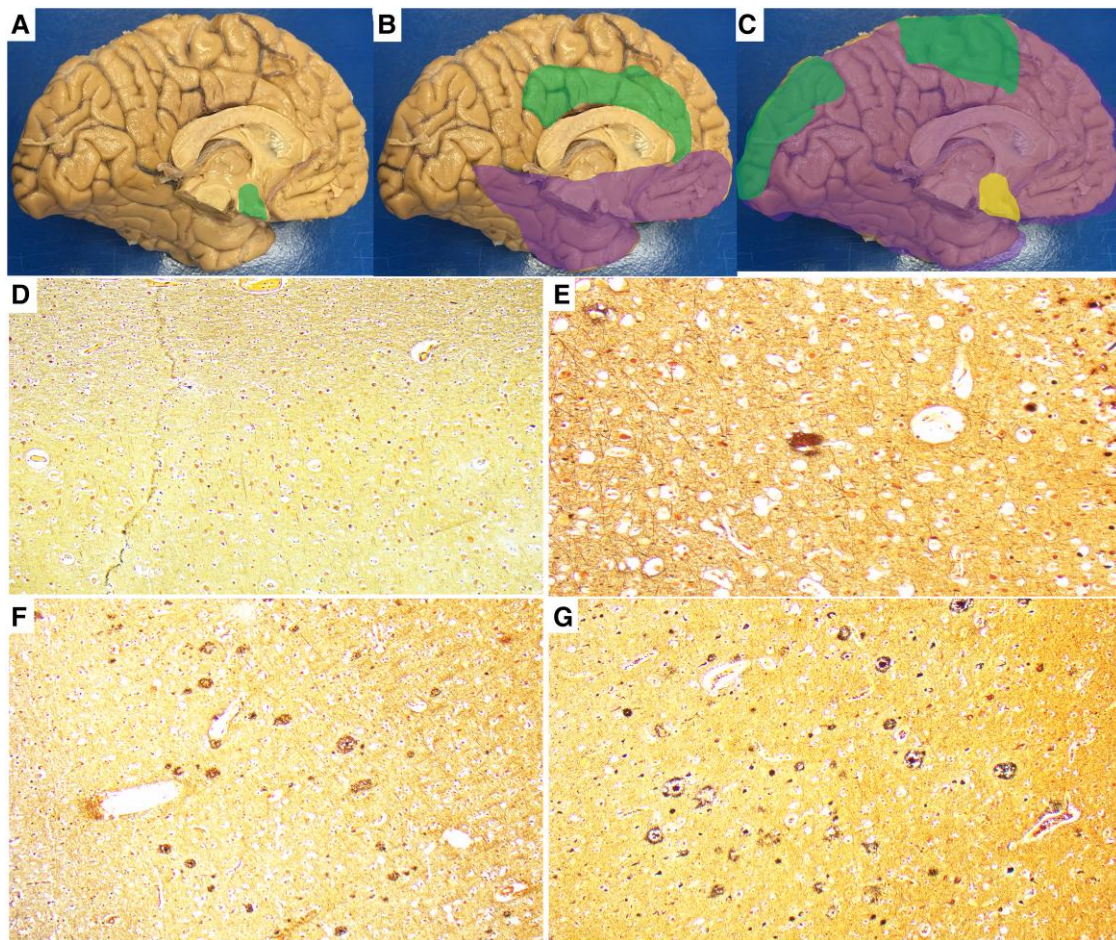


Figure 2 Schematics of Braak staging of neurofibrillary tangles and CERAD score of neuritic plaque density. (A) Stages I and II (transentorhinal) are considered early stages, with the involvement of mesial temporal structures (hippocampus and entorhinal cortex), as demonstrated by the green highlight. **(B)** In Stages III and IV (limbic), neurofibrillary tangles spread beyond mesial temporal structures to involve the lingual gyrus, fusiform gyrus and neocortical association cortices. **(C)** In Stages V and VI (neocortical), neurofibrillary tangles have more widespread involvement in most of the neocortical areas. **(D)** C0: none, absence of neuritic plaques. **(E)** C1: sparse, 1–5 neuritic plaques per 1 mm². **(F)** C2: moderate, ≥6 neuritic plaques and <20 neuritic plaques per 1 mm². **(G)** C3: frequent, ≥20 neuritic plaques per 1 mm². The brain used for A–C is the healthy brain of a 59-year-old male who died of pneumonia. Green shading is used to indicate mild involvement, purple shading to indicate moderate involvement, and yellow shading to indicate severe involvement. Bieckshovsky stain is used to demonstrate neuritic plaque density in D–G. CERAD = Consortium to Establish a Registry for Alzheimer’s Disease.

and ethnicity (Hispanic versus non-Hispanic) were compared among the three seizure groups. The severity of cognitive impairment at the most recent follow-up visit before death based on the Clinical Dementia Rating score (CDR-global) was also compared among the seizure groups¹⁶ (CDR-global scores: 0 = healthy cognition, 0.5 = MCI, 1 = mild dementia, 2 = moderate dementia and 3 = severe dementia^{16,17}).

Statistical analysis

Baseline analysis

Baseline demographic and cognitive categorical variables were summarized using frequencies (*n*) and percentages (%), and the mean and standard deviation (SD) described continuous variables (Table 1).

Primary and secondary outcome analysis

Among all deceased participants, relationships between the seizure group and the baseline characteristics (i.e. age at death, sex,

race, education, ethnicity, CDR-global, dementia subtype) were compared by seizure group with Pearson’s χ^2 tests or Fisher’s exact test for categorical variables and ANOVA tests for continuous variables.

Participants with a final primary post-mortem neuropathological diagnosis of AD and non-AD were analysed separately. The presence of co-pathologies was analysed further within each of the two primary neuropathological groups (AD and non-AD). For example, for primary neuropathological diagnosis of AD, co-pathologies of FTD, Lewy body pathology and vascular pathology were analysed. Post hoc analyses were performed to compare findings among participants with active versus remote seizures and active versus no seizures. Variables with an initial analysis *P*-value of <0.1 were included in post hoc analyses. Braak staging was categorized as 0, transentorhinal (I and II), limbic (III and IV), neocortical (V and VI) and Stage 7 during post hoc analyses. Because of extensive contingency tables, Fisher’s exact test with simulated *P*-value (based on 100 000 replicates) was applied to neuropathological outcome categories, using a Monte Carlo simulation approach for initial and post hoc analyses.

Table 1 Demographics and final primary post-mortem neuropathological diagnosis of the autopsied cohort

Demographics	No seizures n = 5640	Remote seizures n = 151	Active seizures n = 294	Overall n = 6085	P-value
Age, years (mean ± SD)	80.4 ± 11.5	76.9 ± 11.1	75.0 ± 12.6	80.0 ± 11.6	<0.001
Education, years (mean ± SD)	15.4 ± 3.18	15.2 ± 3.22	15.0 ± 3.33	15.3 ± 3.19	0.16
Sex					
Male, n (%)	3098 (55%)	83 (55%)	159 (54%)	3340 (55%)	>0.9
Female, n (%)	2542 (45%)	68 (45%)	135 (46%)	2745 (45%)	
Race					
Non-White, n (%)	322 (5.7%)	8 (5.4%)	22 (7.5%)	352 (5.8%)	0.4
White, n (%)	5293 (94%)	141 (95%)	271 (92%)	5705 (94%)	
Ethnicity					
Non-Hispanic, n (%)	5405 (96%)	140 (93%)	276 (95%)	5821 (96%)	0.049
Hispanic, n (%)	206 (3.7%)	10 (6.7%)	16 (5.5%)	232 (3.8%)	
Hypertension, n (%)	2396 (57%)	60 (51%)	107 (46%)	2563 (56%)	0.003
Diabetes, n (%)	505 (12%)	15 (13%)	25 (11%)	545 (12%)	0.8
Active Depression, n (%)	1910 (46%)	58 (51%)	117 (52%)	2085 (46%)	0.095
CDR-Global (mean ± SD)	1.86 ± 1.01	2.07 ± 1.03	2.54 ± 0.82	1.90 ± 1.01	<0.001
Final neuropathological diagnosis					
Primary pathological diagnosis: AD, n (%)	4155 (74%)	113 (75%)	241 (82%)	4509 (74%)	0.008
Primary pathological diagnosis: Non-AD, n (%)	1481 (26%)	38 (25%)	52 (18%)	1571 (26%)	
Non-AD subtypes					
Primary pathological diagnosis: FTD, n (%)	709 (13%)	17 (11%)	19 (6.5%)	745 (12%)	
Primary pathological diagnosis: Lewy body, n (%)	387 (6.9%)	11 (7.3%)	15 (5.1%)	413 (6.8%)	
Primary pathological diagnosis: vascular pathology, n (%)	154 (2.7%)	4 (2.6%)	5 (1.7%)	163 (2.7%)	
Primary pathological diagnosis: other pathology, n (%)	231 (4.1%)	6 (4.0%)	13 (4.4%)	250 (4.1%)	

AD = Alzheimer's disease; CDR = Clinical Dementia Rating; FTD = frontotemporal dementia; SD = standard deviation.

Missing data were excluded from analyses. Significant results were reported using a two-sided alpha level of 0.05. Benjamini-Hochberg false discovery rate correction was made for multiple comparisons among neuropathology findings and seizure groups for all *post hoc* analyses. We used R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.

Results

Clinical characteristics

Those with active seizures experienced higher mortality than those with remote seizures or controls (the proportion of deceased participants within each of the three groups was as follows: active seizure participants = 56%, remote seizure participants = 35%, controls = 34%, $P < 0.001$; [Supplementary Table 1](#)). Of the 10 474 participants who died, 407 had active seizures, 221 had remote seizures, and 9846 participants served as controls ([Fig. 1](#) and [Supplementary Tables 2 and 3](#)). The three groups differed in terms of age at death (active = 75.0 years, remote = 76.9 years and controls = 80.4 years, $P < 0.001$), ethnicity (Hispanics among active seizure participants = 5.5%, remote = 6.7%, controls = 3.7%, $P = 0.049$), hypertension (active = 46%, remote = 51%, controls = 57%, $P = 0.003$) and dementia severity as measured by CDR-global (active = 2.54, remote = 2.07, controls = 1.86, $P < 0.001$) ([Table 1](#)).

Neuropathology on autopsy

A total of 6085 (58.1% of deceased) participants underwent autopsy. Among 6085 who underwent autopsy, 294 had active seizures, 151 had remote seizures, and 5640 had no seizures ([Fig. 1](#)).

Primary post-mortem neuropathological diagnosis of Alzheimer's disease

The severity of Alzheimer's disease pathology

Overall, our results showed that among participants with the primary post-mortem diagnosis of AD, active seizures had an association with more severe neurodegeneration and higher stages of ATN (amyloid, tau and neurodegeneration)¹⁸ neuropathology.

The three seizure groups differed in terms of histopathological markers of AD pathology, including CERAD score for neuritic plaque density and Braak staging for neurofibrillary degeneration ([Supplementary Table 3](#)). In *post hoc* analysis, active seizure participants had higher Braak stages of neurofibrillary degeneration (tau; [Fig. 3](#)) and higher density of neuritic plaques (amyloid; [Fig. 3](#)) than remote seizures and controls ([Supplementary Table 4](#)). No statistically significant differences among groups existed in the Thal phase for amyloid plaques ([Supplementary Table 3](#)).

FTD, Lewy body and vascular co-pathology

In *post hoc* analyses, active seizure participants had significantly less FTD co-pathology than no-seizure controls (see later). No statistically significant differences existed in Lewy body co-pathology among the groups ([Supplementary Table 3](#)). There were no group differences in terms of vascular co-pathology or Circle of Willis atherosclerosis ([Supplementary Table 3](#)).

Neurodegeneration

Among participants with the final primary post-mortem diagnosis of AD, gross cerebral atrophy, hippocampal atrophy and LC hypopigmentation differed among the three seizure groups ([Supplementary Table 3](#)). In *post hoc* analysis, active seizure

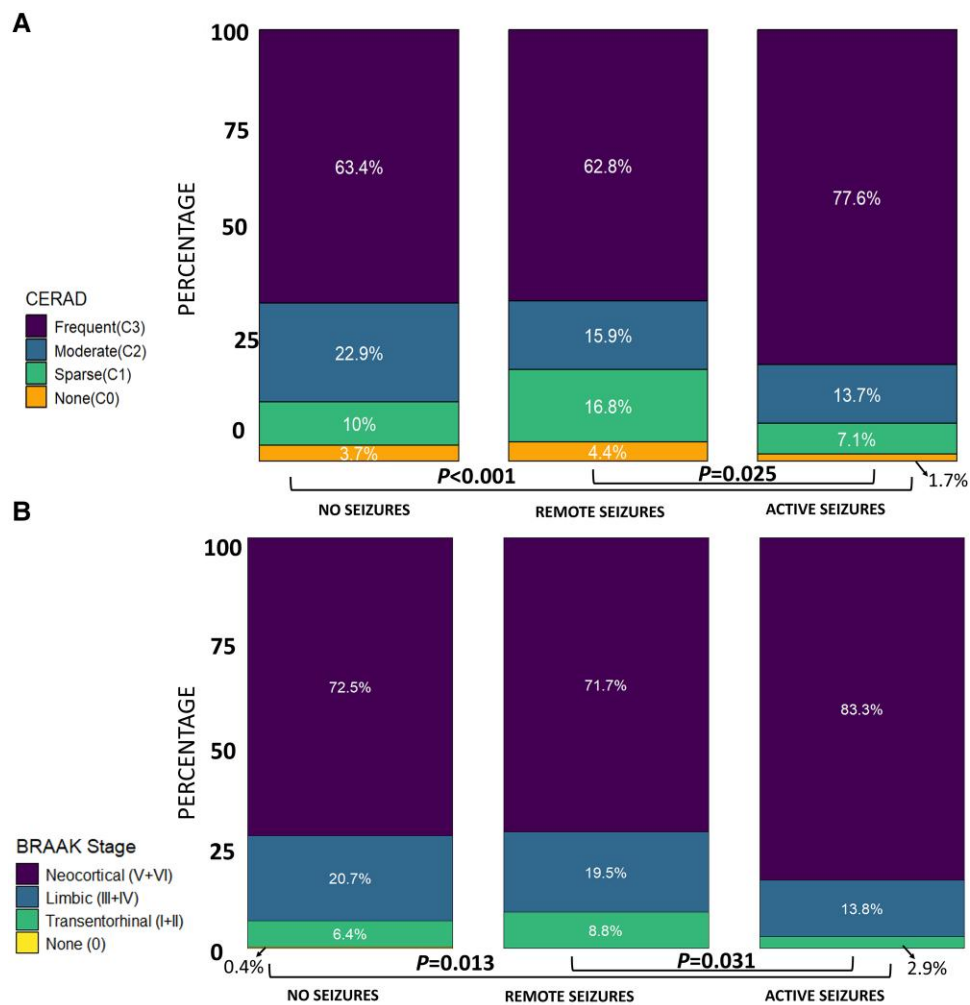


Figure 3 CERAD scores and Braak stages in those with primary post-mortem neuropathological diagnosis of Alzheimer's disease compared among the three groups. (A) CERAD score density of neuritic plaques (amyloid) among the three groups subcategorized into none (C0), sparse (C1), moderate (C2) and frequent (C3). (B) Braak stages of neurofibrillary degeneration (Tau) among the three groups subcategorized as none (Stage 0), transentorhinal (Stage I and II), limbic (Stage III and IV) and neocortical (Stage V and VI). CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

participants had significantly more cerebral atrophy (Fig. 4A), hippocampal atrophy (Fig. 4B) and LC hypopigmentation (Fig. 5) than controls, whereas no statistically significant differences were observed between the active and remote seizure groups (Supplementary Table 4). Although not statistically significant, the proportion of active seizure participants with some degree of cerebral atrophy (active = 92%, remote = 87%) and hippocampal atrophy (active seizures = 86% versus remote seizures = 80%) was higher than those with remote seizures. There were no group differences in lobar atrophy and substantia nigra hypopigmentation (Supplementary Table 3).

Primary post-mortem neuropathological diagnosis of non-Alzheimer's disease

Alzheimer's disease co-pathology

Among participants with the final post-mortem diagnosis of non-AD, AD co-pathology was assessed via the Thal phase of A β plaques, Braak staging for tau and CERAD score of neuritic plaque density. In post hoc analyses, active seizure participants had higher

Braak stages of neurofibrillary degeneration (tau; Fig. 6A) than remote seizures and controls. Active seizure participants also had a higher Thal phase of A β plaques than remote seizure participants (Fig. 6B and Supplementary Table 5).

FTD, Lewy body and vascular pathology

Among participants with the final primary post-mortem diagnosis of non-AD, in post hoc analyses, active seizure participants had significantly less FTD pathology (Fig. 7) than no-seizure controls (Supplementary Table 5). No statistically significant differences existed in Lewy body pathology, vascular pathology or Circle of Willis atherosclerosis among the groups (Supplemental Table 3).

Neurodegeneration

Among participants with the final post-mortem diagnosis of non-AD (Supplementary Table 6), there were no group differences in gross cerebral atrophy, lobar atrophy, hippocampal atrophy and brainstem neurodegeneration (LC hypopigmentation and substantia nigra hypopigmentation).

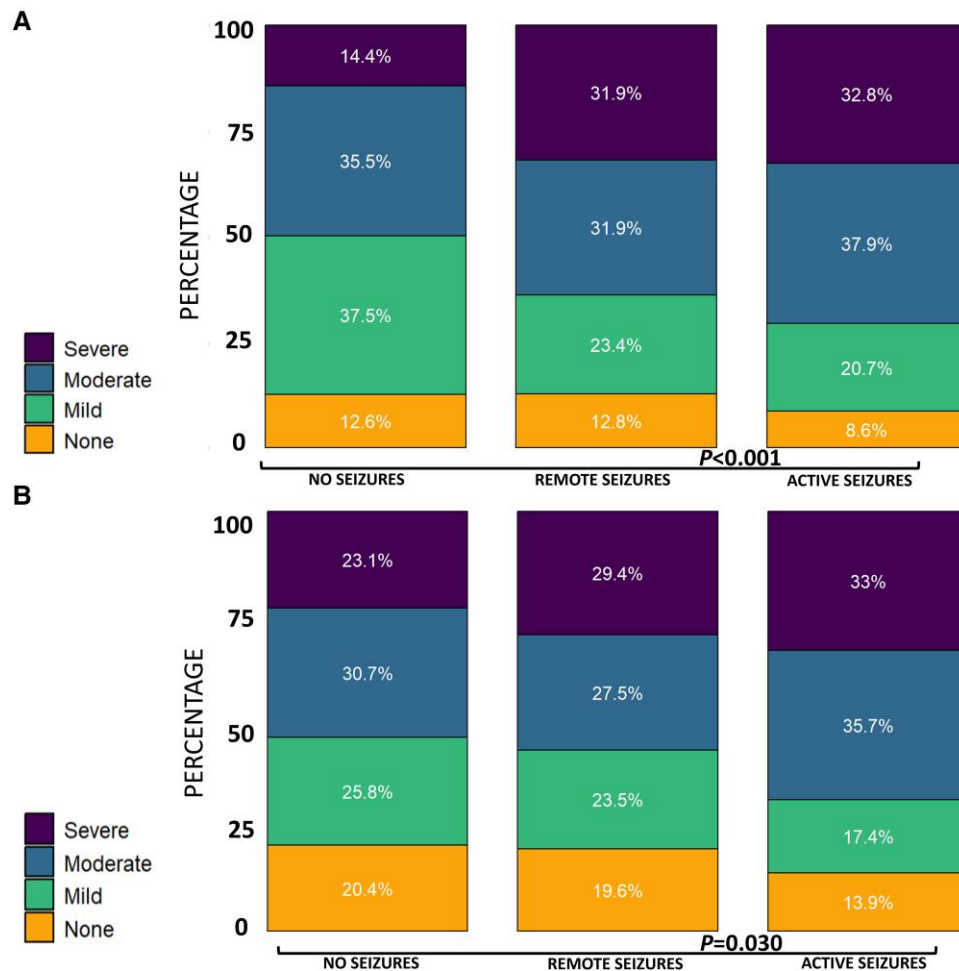


Figure 4 The severity of neurodegenerative findings in those with primary post-mortem diagnosis of Alzheimer's disease compared among the three groups. (A) The severity of gross cerebral atrophy (neurodegeneration) among the seizure groups subcategorized as none, mild, moderate and severe. (B) The severity of hippocampal atrophy (neurodegeneration) among the seizure groups subcategorized as none, mild, moderate and severe.

Discussion

In this cross-sectional, post-mortem analysis of PWD, we found that among participants with the primary post-mortem diagnosis of AD, active seizures were associated with more severe neurodegeneration and higher stages of ATN¹⁸ neuropathology, demonstrated by higher Braak stage for neurofibrillary degeneration (tau), higher density of neocortical neuritic plaque (amyloid), significantly more cerebral atrophy (neurodegeneration), hippocampal atrophy (neurodegeneration) and LC hypopigmentation (neurodegeneration), than those with remote and/or no seizures. Our findings also showed that among participants with the primary post-mortem diagnosis of non-AD, active seizures were associated with higher stages of amyloid and tau, demonstrated by higher Braak stages for neurofibrillary tau tangles and higher Thal phases of A β plaques. These findings suggest that active seizures are associated with more advanced AD pathology in AD and worse AD co-pathology in non-AD.

The most important and novel contribution of our study is that we differentiated active from remote seizures, thereby directly comparing neuropathology findings between active seizures and resolved seizures. We found that although active seizure participants died at a younger age compared with other groups, they

had greater cognitive deficits and accelerated ATN progression. The observed differences in neuropathological markers, such as more severe AD pathology and worse neurodegeneration evident from cortical and hippocampal atrophy in the active seizure group, raise the possibility that uncontrolled seizures might exacerbate neurodegeneration. However, causality cannot be determined in our cross-sectional study, and the reverse relationship is also possible. Hence, it is also possible that seizures are a result of more advanced neurodegeneration rather than contributing to it. More severe neurodegenerative processes, including amyloid plaque deposition, neurofibrillary tangles and neuronal loss, might create an environment conducive to epileptogenesis, resulting in ongoing seizures.

Our findings of higher Braak stages in those with active seizures suggest that ongoing seizures are associated with more advanced neurofibrillary degeneration. Evidence indicates that seizures and tau secretion interact bidirectionally; seizures increase tau secretion, and tau secretion induces seizures.¹⁹ Conversely, tau reduction might reduce seizure burden and severity.¹⁹ Our findings support earlier studies that linked seizure activity to accelerated tau pathology. For instance, Tai *et al.*²⁰ demonstrated that temporal lobe tissue resected from people with epilepsy who underwent epilepsy surgery, compared with non-epileptic controls, exhibited

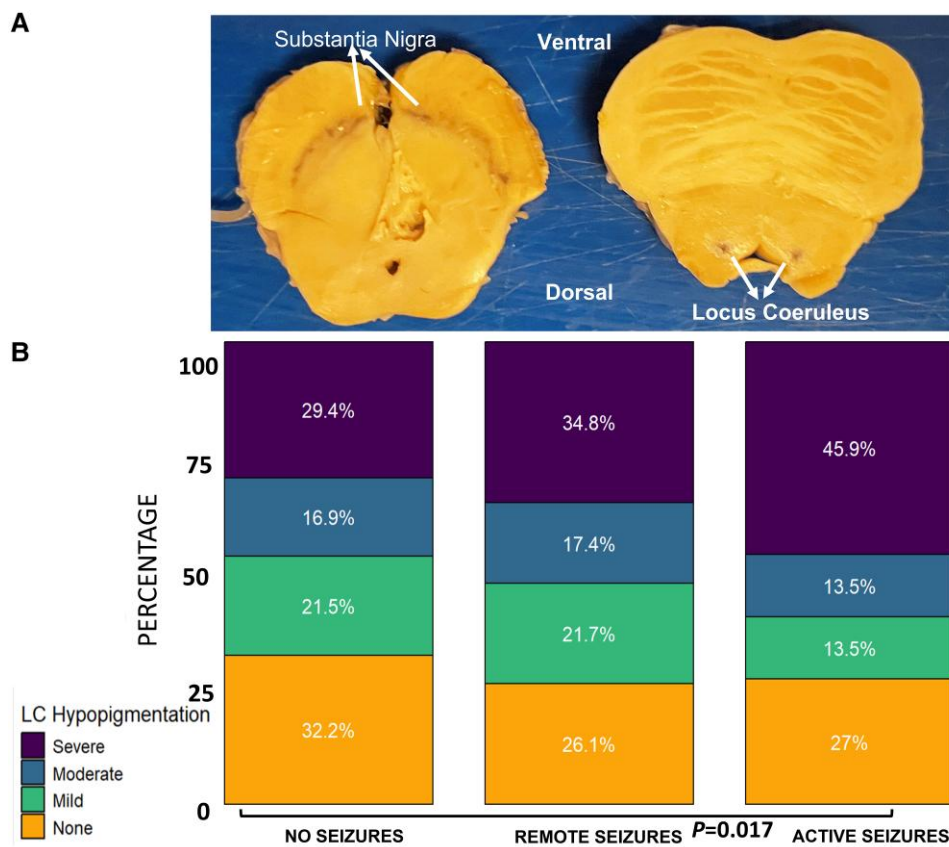


Figure 5 The severity of brainstem neurodegeneration in those with primary post-mortem diagnosis of Alzheimer's disease compared among the three groups. (A) Schematic diagram of a brainstem section showing a normal substantia nigra and normal locus coeruleus in a 59-year-old male with a healthy brain who died of pneumonia. (B) The severity of locus coeruleus hypopigmentation among the three groups. The subcategories of none, mild, moderate and severe were used to assess the severity of locus coeruleus hypopigmentation. LC = locus coeruleus.

increased tau accumulation and higher Braak stages. Furthermore, the degree of tau was associated with postoperative cognitive outcomes.²⁰ Prolonged seizure activity can disrupt normal protein clearance mechanisms, contributing to the accumulation of hyperphosphorylated tau and progression through Braak stages.²¹ Animal models have shown that recurrent seizures can upregulate kinases responsible for tau phosphorylation, such as glycogen synthase kinase-3 β , leading to accelerated tangle formation.²² The increased neurofibrillary degeneration observed in active seizure participants might also be attributed to seizure-induced neuronal stress, excitotoxicity and hyperphosphorylation.¹⁹ Likewise, neurofibrillary tangles and tau aggregates have pro-epileptogenic properties, and they can induce epileptogenesis and neuronal hyperexcitability, leading to an increased likelihood of ongoing seizures.²³

As with tau, the present study shows an association between increased A β aggregation and a higher density of neocortical neuritic plaques and active seizures. A β aggregates can induce seizure activity, and ongoing seizures can worsen A β burden. A β aggregates can induce hyperexcitability in cortical and hippocampal tissue, increase glutamate and reduce γ -aminobutyric acid, thereby leading to seizures.²³ Our study also supports the findings of animal studies that demonstrated a higher burden of A β aggregation and neuritic plaques in the presence of seizures and that epileptiform activity can promote A β aggregation.^{8,24} A potential mechanism is that the increased, unregulated neuronal activity from seizures promotes elevated production and impaired clearance of A β peptides.

Animal studies have demonstrated that heightened synaptic activity, such as during seizures, can increase A β generation and deposition through activity-dependent processing of amyloid precursor protein and altered synaptic vesicle exocytosis.²⁵ Furthermore, seizures might disrupt the glymphatic clearance system, probably reducing the removal of extracellular A β and, in turn, facilitating plaque formation.²⁶

Our finding of worse global cortical atrophy in active seizure participants with primary post-mortem diagnosis of AD suggests that cortical atrophy might contribute to or worsen ongoing seizures, especially in AD. An insult to the brain, trauma or other neurodegenerative processes leading to cortical atrophy are known to increase the risk of seizures.²⁷ Another possible explanation for the association between more severe cortical atrophy and active seizures in our study is a neurodegenerative effect of ongoing seizures, which agrees with earlier studies that show widespread cortical thinning and volume loss in patients with chronic epilepsy.²⁸ Bernhardt et al.²⁹ observed progressive cerebral atrophy in temporal lobe epilepsy over time, suggesting a neurodegenerative component associated with ongoing seizures. McDonald et al.³⁰ found that atrophy was predominantly confined to bilateral frontotemporal regions, with some asymmetric atrophy more prominent ipsilateral to the seizure focus. Some prospective studies have revealed significant frontotemporal cortical thinning associated with ongoing seizures, which improved with better seizure control following epilepsy surgery.^{28,31} Likewise, the presence of motor seizures was associated with more neuronal loss on autopsy in PWD

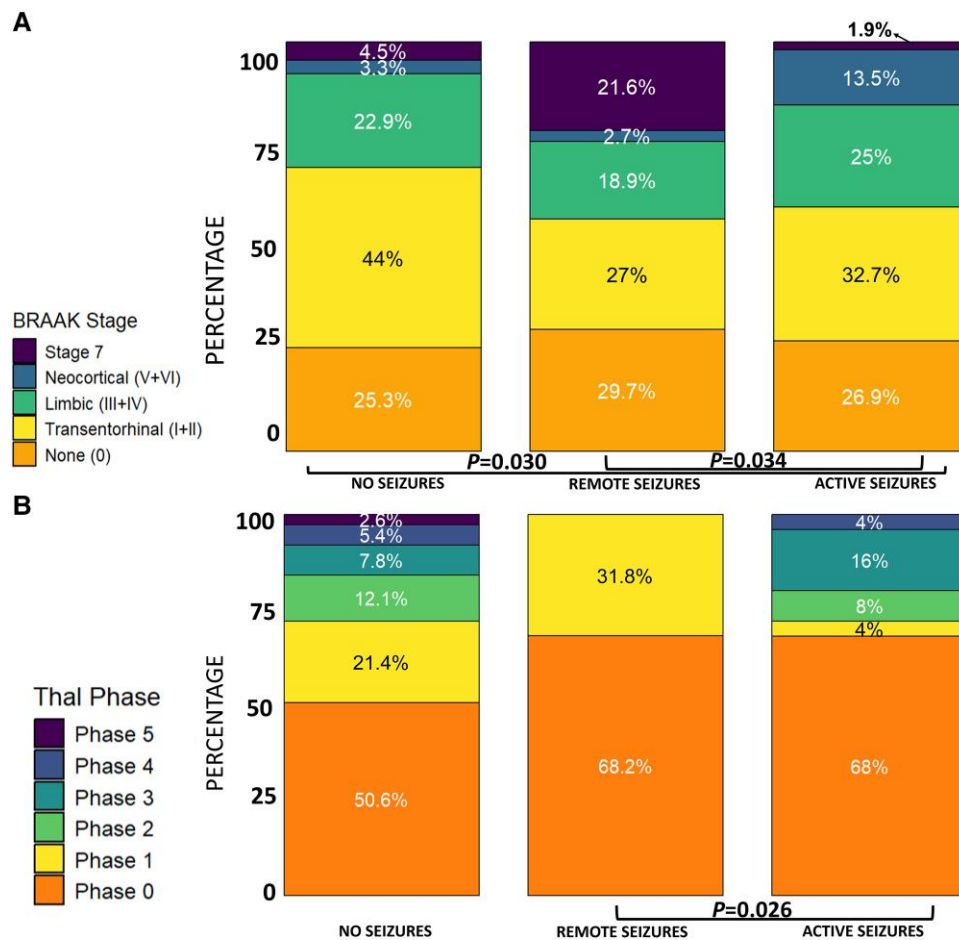


Figure 6 Braak stages and Thal phases in those with primary post-mortem neuropathological diagnosis of non-Alzheimer's disease compared among the three groups. (A) Braak stages of neurofibrillary degeneration (Tau) among the three groups subcategorized as none (Stage 0), transentorhinal (Stages I and II), limbic (Stages III and IV) and neocortical (Stages V and VI), and Stage 7 [the presence of a tauopathy (other than ageing/AD) precludes Braak staging]. (B) Thal phase of amyloid plaques among the three groups subcategorized as Phase 0, 1, 2, 3, 4 or 5. AD = Alzheimer's disease.

than the absence of motor seizures.^{19,24} One possible mechanism that drives cerebral atrophy in active seizures is the effect of seizure-associated excitotoxic neuronal injury, chronic inflammation and oxidative stress.³²

We also found more pronounced hippocampal atrophy, in active seizure participants compared with controls, in those with primary AD. Early hippocampal atrophy, neuronal loss and gliosis are the key features of AD pathology.³³ Hippocampal damage and atrophy, in turn, serve as a precursor to seizures, and hippocampal neuronal death promotes the progression of epileptogenesis and seizures.³⁴ Therefore, the findings of more severe hippocampal atrophy in AD with active seizure are not surprising. However, the association between hippocampal atrophy and ongoing seizures is likely to be bidirectional. There is extensive literature linking ongoing seizure activity to hippocampal neurodegeneration. Significant hippocampal volume loss has been demonstrated in temporal lobe epilepsy, often associated with prolonged seizure histories.³⁵ Repeated focal seizures can lead to rapidly progressive hippocampal atrophy,³⁶ correlating with cognitive deficits, particularly in memory function.¹⁹ The hippocampus is highly susceptible to excitotoxic damage owing to its dense glutamatergic circuitry. Excess glutamate release during prolonged or recurrent seizures can lead to sustained depolarization, *N*-methyl-D-aspartate receptor

activation, calcium influx and neuronal apoptosis, predominantly impacting CA1 pyramidal cells and the hilus of the hippocampus and subsequent hippocampal atrophy.³⁷ Additionally, programmed cell death mechanisms involving calpain activation and mitochondrial dysfunction contribute further to this hippocampal damage.³⁷

Our findings of neuronal loss in the brainstem (hypopigmentation of the LC) in the active seizures group have less precedence. The LC is known to limit the propagation of seizures and the duration of various seizure types.³⁸ Damage to the LC is associated with increased seizure susceptibility and severity in animal models and can lead to prolonged episodes of status epilepticus, and brainstem atrophy is associated with worse outcomes, including sudden unexpected death in epilepsy.^{39,40} The LC plays an anti-epileptic role in vagus nerve stimulation, and the anti-epileptic effect of vagus nerve stimulation might be reduced with the loss of LC activity. It is hypothesized that the LC is responsible for adrenergic input to the hippocampus and cortex in such a fashion that increased LC activity inhibits seizures.⁴¹ In contrast, convulsions in rats are associated with increased LC activity, resulting in noradrenaline depletion,⁴² which can, in turn, exacerbate seizure activity by reducing inhibitory circuits, creating a detrimental feedback loop. The presence of LC hypopigmentation might

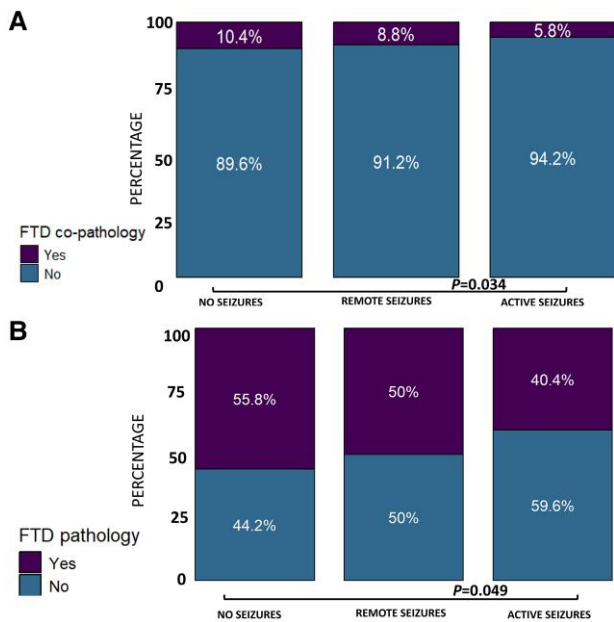


Figure 7 Frontotemporal lobar neurodegeneration compared among the three groups. (A) The presence or absence of frontotemporal lobar neurodegeneration co-pathology in participants with primary post-mortem diagnosis of AD compared among the three seizure groups. **(B)** The presence or absence of frontotemporal lobar neurodegeneration pathology in participants with primary post-mortem diagnosis of non-AD compared among the three seizure groups. AD = Alzheimer's disease; FTD = frontotemporal lobar degeneration.

have played a role in poor seizure control in these participants in our study.

We also found that active seizures were less commonly observed in participants with histopathological evidence of FTD in those with primary post-mortem diagnoses of AD and non-AD. Seizures in FTD remain understudied, and the evidence for an association between the two entities remains controversial. Although some studies have noted a similar prevalence of seizures in FTD and AD,⁴³ others have reported an overall much lower prevalence of seizures in FTD.⁴⁴ These findings highlight the need for larger, more robust prospective studies in the future to investigate seizures in FTD.

The three groups differed in CDR, with active seizure participants showing higher CDR scores, indicating worse cognition. The CDR differences noted among the groups could be explained by the underlying neuropathological differences found on autopsy, because a higher tau burden, as demonstrated by the Braak stage, and higher amyloid burden, as evident from the CERAD score and more significant neurodegeneration, would also translate into worse cognition and worse CDR scores in those with active seizures. However, active seizure participants were also taking ASMs, which can also have cognitive side effects and impact CDR.

A significant strength of our study is that it expands the existing knowledge through its relatively large sample size, the inclusion of control participants monitored under the same protocol, and clinician-conducted longitudinal diagnostic evaluations. However, our study has several limitations. We had limited information regarding seizures. Although seizure aetiology, type, burden and severity might be associated with neurodegeneration,^{4,45} the ADCRs did not collect specific data on epilepsy or EEG. Our

extensive, prospectively collected data cannot establish cause versus effect. Although people with active seizures had more neurodegeneration in comparison to those with remote seizures, active seizures could simply signal later stages of dementia and more severe neurodegeneration. It could be possible that active seizures are a manifestation of worse neurodegeneration rather than seizures contributing to worse neuropathological outcomes. Therefore, future studies are needed to elucidate this relationship further.

There is an inherent limitation in how 'active seizures' are defined. Active seizure participants were those who either had recurrent seizures and/or required ongoing ASM treatment. Some of these participants might have better seizure control than others. Therefore, the association between seizure frequency or the degree of seizure control and neuropathological findings could not be assessed. The study's participants were followed annually, and their seizure status was documented at each visit. Because the number of visits for each participant varied, ranging from 1 to 17 visits, we adopted a uniform definition of active seizures as those occurring within the 12 months prior to the visit, although the duration of active seizures could have been much longer in many participants. Moreover, the duration of ASM use was also largely missing. Therefore, our study could not accurately analyse the true duration of reported active seizures. The impact of variable seizure duration on the results of our study remains uncertain. More severe and frequent seizures can cause head injury, and injury to the head can, in turn, trigger a tau cascade, worsening tau pathology.⁴⁶ Moreover, seizure severity is determined not only by the presence of seizures in the past year but also by the number of seizures, number of ASMs, number of emergency department visits, and episodes of status epilepticus. However, these data were not available for our study.

Seizures are often subtle, under-recognized and underreported in the context of dementia.⁴⁷ Therefore, despite clinician-conducted assessments, the true occurrence of ongoing seizures is likely to be underestimated in our study. The exact timing of the seizure onset and resolution for the remote seizures group was not collected as a part of the study and was therefore not available. Many participants lack autopsy, and the possible selection bias is unknown. Missing data might have impacted the results of our analyses. Lastly, the study participants were recruited at tertiary, specialized memory disorder centres, which might affect the generalizability of our results.

Conclusion

In summary, our findings suggest that active seizures, compared with remote seizures before death, are associated with post-mortem evidence of higher stages of AD pathology, ATN and more severe neuropathology. Active seizures appear linked to more advanced ATN pathology not only in AD, but also worse AD co-pathology in non-AD dementias. Our findings add to the growing evidence of the interplay between seizures and dementia attributable to AD. Advanced and more severe neurodegeneration can lead to seizures, and ongoing seizures, in turn, have the potential to worsen neurodegeneration. However, causality cannot be established from the results of our study, and further large-scale prospective studies are essential to clarify this relationship. Clinicians should be vigilant in detecting seizures in PWD, because this could signal a worse prognosis in individuals with dementia.

Data availability

Data used to prepare this article were obtained from the National Alzheimer's Coordinating Centre database. For up-to-date information on the study, visit <https://naccdata.org/requesting-data/nacc-data>. All data used in this study, in addition to a data dictionary, are available on the website. Additional related documents, including the study protocol and assay methods, are also available. Data access can be requested on the website.

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Competing interests

The authors report no competing interests.

Supplementary material

[Supplementary material](#) is available at [Brain online](#).

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